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Dated: November 22, 2010
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: RUJ-001CNCPRCE2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ralph Steinman *et al.*

Application No.: 09/925,284 Art Unit: 1644

Filed: August 9, 2001 Examiner: Ronald B. Schwadron

For: ENHANCED ANTIGEN DELIVERY AND MODULATION OF THE IMMUNE RESPONSE THEREFROM

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Dear Sir:

Appellants hereby appeal the final decision of the Examiner in the above-identified application rejecting the subject matter of the pending claims. For the reasons set forth in this Brief, Appellants respectfully request the Board of Patent Appeals and Interferences reverse the Examiner's final rejection of the claimed subject matter. A Request for Extension of Time for three months is submitted herewith.

This brief contains items under the following headings as required by 37 C.F.R. §41.37 and M.P.E.P. §1205.2:

I. REAL PARTY IN INTEREST

The real parties in interest in the above-identified application are Rockefeller University, the assignee of the application, and Celldex Therapeutics, Inc., the licensee of the application.

II. RELATED APPEALS AND INTERFERENCES

An Appeal Brief was filed in U.S.S.N.:09/586704, having a filing date of June 5, 2000. However, the Appeal Brief was not considered by the Board of Patent Appeals and Interferences and, instead, the Examiner re-opened prosecution. An Amendment and Response After Final was filed in U.S.S.N.:09/586704 on October 25, 2010.

No related interferences are known to Appellants, which will directly affect, or be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1-21 are pending in this application. Claims 1-5 and 10-12 have been withdrawn from consideration.

Claims 6-9 and 13-21 are on appeal and are set forth in the Claims Appendix (Appendix A).

IV. STATUS OF THE AMENDMENTS

All prior amendments have been entered. Claims 6-9 and 13-21 are on appeal and are set forth in the Claims Appendix (Appendix A).

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 6-9

Claims 6-9 on appeal are drawn to methods for enhancing tolerance to a preselected antigen in a mammal, comprising exposing *ex vivo* or *in vivo* dendritic cells from the mammal to a vaccine conjugate that comprises the preselected antigen covalently bound to an anti-human DEC-205 antibody, or an anti-murine DEC-205 antibody that binds to human DEC-205, under conditions that promote dendritic cell quiescence, wherein the human DEC-205 protein comprises the amino acid sequence of SEQ ID NO: 7. The amino acid sequence of SEQ ID NO:7 corresponds to a partial (C-terminal) sequence of human DEC-205 (see, for example, page 11, lines 1-16; page 18,

lines 5-10; page 25, line 16 through page 26, line 5; page 27, lines 13-17 of the specification as originally filed).

Dependent claims 7-9 on appeal do not stand or fall together with independent claim 6, or with each other, because the scope of each dependent claim differs from the independent claim, and from each other. In particular, dependent claims 7-9 do not stand or fall together because they include additional features not required by independent claim 6. Specifically, dependent claim 7 specifies that the preselected antigen is a peptide antigen or a protein antigen. Support for dependent claim 7 can be found, at least, for example, in original claim 7 and at page 7, lines 1-10; page 8, line 22 through page 9, line 2 of the specification as originally filed. Dependent claim 8 specifies that the peptide or protein is conjugated to the anti-DEC-205 antibody via a cross-linking agent. Support for dependent claim 7 can be found, at least, for example, in original claim 8 and at page 6, lines 4-14 of the specification as originally filed. Dependent claim 9 specifies that the light or heavy chain of the anti-DEC-205 antibody and the antigen are present on a single polypeptide chain. Support for dependent claim 7 can be found, at least, for example, in original claim 9 and at page 8, line 22 through page 9, line 2 of the specification as originally filed. Accordingly, the claims do not stand or fall together, and the inquiry as to whether claims 6-9 are properly rejected under 35 U.S.C. § 112, first paragraph, differs for each and every claim on appeal.

Claims 13-17

Claims 13-17 on appeal are drawn to methods for enhancing tolerance to a preselected antigen for which tolerance is desired in a mammal, comprising exposing *ex vivo* or *in vivo* dendritic cells from said mammal to a conjugate comprising said preselected antigen covalently bound to an anti-human DEC-205 antibody (claim 13) or anti-murine DEC-205 antibody (claim 14), wherein the antibody is reactive with an amino acid sequence as set forth in SEQ ID NO: 7. As noted above, the amino acid sequence of SEQ ID NO:7 corresponds to a partial (C-terminal) sequence of human DEC-205 (see, for example, page 11, lines 1-16; page 18, lines 5-10; page 25, line 16 through page 26, line 5; page 27, lines 13-17 of the specification as originally filed).

Dependent claims 15-17 on appeal do not stand or fall together with independent claims 13 and/or 14, or with each other, because the scope of each dependent claim differs from the independent claims, and from each other. In particular, dependent claims 15-17 do not stand or fall together because they include

additional features not required by independent claims 13 or 14. Specifically, dependent claim 15 specifies that the preselected antigen is a peptide antigen or a protein antigen. Support for dependent claim 15 can be found, at least, for example, in original claim 7 and at page 7, lines 1-10; page 8, line 22 through page 9, line 2 of the specification as originally filed. Dependent claim 16 specifies that the peptide or protein is conjugated to the anti-DEC-205 antibody via a cross-linking agent. Support for dependent claim 16 can be found, at least, for example, in original claim 8 and at page 6, lines 4-14 of the specification as originally filed. Dependent claim 17 specifies that the light or heavy chain of the anti-DEC-205 antibody and the antigen are present on a single polypeptide chain. Support for dependent claim 17 can be found, at least, for example, in original claim 9 and at page 8, line 22 through page 9, line 2 of the specification as originally filed. Accordingly, the claims do not stand or fall together and the inquiries as to whether claims 13-17 are properly rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement differs for each and every claim on appeal.

Claims 18-21

Claims 18-21 on appeal are drawn to methods for enhancing tolerance to a preselected antigen in a mammal comprising exposing *ex vivo* or *in vivo* dendritic cells from the mammal to a conjugate comprising the preselected antigen bound to an anti-mouse DEC-205 antibody that cross-reacts with human DEC-205, under conditions that promote dendritic cell quiescence, wherein the mouse DEC-205 protein comprises the amino acid sequence of SEQ ID NO: 10. The amino acid sequence of SEQ ID NO:10 corresponds to the full-length sequence of mouse DEC-205 (see, for example, page 11, lines 1-16; page 18, lines 5-10; page 25, line 16 through page 26, line 5; page 27, lines 13-17 of the specification as originally filed).

Support for the full length mouse DEC-205 sequence (SEQ ID NO: 3) also can be found in the parent application, U.S.S.N. 09/586,704, which is incorporated by reference in its entirety in the present application, U.S.S.N. 09/925,284. Additionally, support can be found in the Substitute Sequence Listing submitted in the present application on December 22, 2005, which identifies the full length mouse DEC-205 sequence as SEQ ID NO: 10.

Dependent claims 19-21 on appeal do not stand or fall together with independent claim 18, or with each other, because the scope of each dependent claim

differs from the independent claim, and from each other. In particular, dependent claims 19-21 do not stand or fall together because they include additional features not required by independent claim 18. Specifically, dependent claim 19 specifies that the preselected antigen is a peptide antigen or a protein antigen. Support for dependent claim 19 can be found, at least, for example, in original claim 7 and at page 7, lines 1-10; page 8, line 22 through page 9, line 2 of the specification as originally filed. Dependent claim 20 specifies that the peptide or protein is conjugated to the anti-DEC-205 antibody via a cross-linking agent. Support for dependent claim 20 can be found, at least, for example, in original claim 8 and at page 6, lines 4-14 of the specification as originally filed. Dependent claim 21 specifies that the light or heavy chain of the anti-DEC-205 antibody and the antigen are present on a single polypeptide chain. Support for dependent claim 21 can be found, at least, for example, in original claim 9 and at page 8, line 22 through page 9, line 2 of the specification as originally filed. Accordingly, the claims do not stand or fall together and the inquiries as to whether claims 19-21 are properly rejected under 35 U.S.C. § 112, first paragraph, differs for each and every claim on appeal.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants present the following issue for review:

1. Whether claims 6-9 and 18-21 are properly rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

2. Whether claims 6-9 are properly rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

3. Whether claims 6-9 and 13-21 are properly rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement.

VII. ARGUMENTS

A. Summary of Examiner's Rejection of Claims 6-9 and 18-21 Under 35 U.S.C. § 112, First Paragraph, as Failing to Comply with the Written Description Requirement

The Examiner has rejected claims 6-9 and 18-21 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular,

the Examiner asserts that the specification does not provide adequate written description for the claimed invention because, while the specification discloses the full length sequence of murine DEC-205 protein, it only discloses a partial sequence for human DEC-205. The Examiner asserts that, because human DEC-205 is approximately 1800 amino acids in length, the recitation in the claim of a 30 or 25 amino acid sequence derived from human DEC-205 does not provide adequate written description of a molecule that is almost 1800 amino acids in length. The Examiner further asserts that the claims encompass antibodies that bind any immunogenic epitope on the approximately 1750 undisclosed amino acids of DEC 205, and that the term human DEC-205 presumably encompasses full length human DEC-205, as well as undescribed mutants and alleles of human DEC-205.

B. Appellants' Response

1. Each Independent Claim Requires Separate Consideration

Appellants respectfully disagree with the Examiner's rejection. As a preliminary matter, the scope of claims 6-9 and 18-21 varies and, as such, the assertions made by the Examiner are not equally applicable to all of these claims.

Specifically, the fact that the present specification teaches a partial human DEC-205 sequence is irrelevant with respect to claims 18-21, since these claims are drawn to methods employing antibody conjugates that bind to *full length murine DEC-205 protein*, the full length sequence of which is provided by Appellants as SEQ ID NO: 10. Thus, the Examiner's statement that the antibody conjugates of claims 18-21 bind to "undisclosed amino acids of DEC 205" is incorrect. Again, the full length sequence of murine DEC-205 is explicitly provided in the present application as SEQ ID NO: 10. Moreover, while the antibody conjugates of claims 18-21 also cross-react with human DEC-205, the epitopes of human DEC-205 that the conjugates bind to are thus, by definition, shared with (*i.e.*, cross-reactive with) murine DEC-205. As such, the sequence of these epitopes is provided as part of the full length murine DEC-205 sequence recited in the claims (SEQ ID NO:10).

Further, with respect to claims 6-9, drawn to methods which employ antibody conjugates that bind to human DEC-205 protein comprising the partial amino acid sequence of SEQ ID NO:7, Appellants respectfully submit that while Appellants' specification does not recite the full length human DEC-205 sequence, or the sequence

of each and every variant of human DEC-205, this does not *de facto* mean that the pending claims fail to comply with the written description requirement. Importantly, it is well-established that the written description standard is not a bright line test, but instead takes into consideration a number of different factors. As discussed in detail below, Appellants' disclosure of the partial human DEC-205 sequence and the full length murine DEC-205 sequence, in combination with knowledge available in the art, were sufficient to demonstrate to one of ordinary skill that they had full possession of the complete human DEC-205 protein, and antibody conjugates against the protein, at the time the present application was filed.

2. The Disclosure of a Fully Characterized Antigen Satisfies the Written Description Requirement

The Written Description requirement may be satisfied if the disclosed function of the claimed invention (*e.g.*, antibody binding) sufficiently correlates to a particular, known structure. Specifically, the Federal Circuit in *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004) concluded that "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen."

Claims 14-21 are drawn to methods employing antibody conjugates that ***bind to full length murine DEC-205 protein*** (SEQ ID NO: 10) and cross-react with either an amino acid sequence as set forth in SEQ ID NO: 7, *i.e.*, a partial (C-terminal) sequence of human DEC-205 (claim 14) or human DEC-205 (claim 18). As discussed above, the full length sequence of murine DEC-205 is explicitly provided in the present application as SEQ ID NO: 10. As such, the antibodies encompassed by claims 14-21, which bind murine DEC-205 protein, clearly meet the written description standard set forth in *Noelle v. Lederman*. Moreover, while the antibody conjugates of claims 14-21 also cross-react with human DEC-205 (or a partial sequence thereof), the epitopes of human DEC-205 that the conjugates bind to are thus, by definition, shared with (*i.e.*, cross-reactive with) murine DEC-205. As such, the sequence of these epitopes is provided as part of the full length murine DEC-205 sequence recited in the claims (SEQ ID NO:10).

3. The Structure and Function of Human DEC-205 Correlates to the Structure and Function of Mouse DEC-205 Protein

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, *e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306 (Fed. Cir. 2003) and *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). Further, as originally articulated by the Federal Circuit in *The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997), and recently affirmed in *Carnegie Mellon University v. Hoffman-La Roche*, 541 F.3d 1115 (Fed. Cir. 2008), a claim to a genus satisfies the written description requirement when its accompanying specification either (1) defines by sequence a representative number of its members falling within the scope of the genus or (2) when its accompanying specification defines the structural features common to a substantial portion of the genus.

In the present case, the structure and function of human DEC-205 clearly correlates to that of mouse DEC-205, the characteristics of which (including full-length sequence) are described in detail in the present disclosure. Accordingly, the fact that Appellants provide an in-depth characterization of mouse DEC-205, including its full-length sequence, which correlates to human DEC-205, as well as a partial (C-terminal) amino acid of human DEC-205, provides further basis for fully meeting the Written Description requirement.

In sum, the teachings set forth in Appellants' specification, in combination with the high level of skill and knowledge in the art at the time of the invention, and the proven predictability of the technologies involved in the invention (discussed below), clearly satisfies the written description standard established by the Federal Circuit (*e.g.*, *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991), *The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997), *Carnegie Mellon University v. Hoffman-La Roche*, 541 F.3d 1115, and *Noelle v. Lederman*, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004)) and demonstrates possession of the claimed invention.

4. The Descriptive Text Needed to Satisfy the Written Description Standard Must be Considered in Relation to the Scientific Knowledge in Existence at the time of the Invention, the Skill in the Art, and Correlation of a Disclosed Function to a Known Structure

The mere fact that Appellants' specification does not recite the full length human DEC-205 sequence does not alone mean that any of the claims on appeal fail to comply with the written description requirement.

Moreover, Appellants respectfully disagree with the Examiner's assertion that the decision in *Capon v. Eshhar* (418 F.3d 1349, 1357 (Fed. Cir. 2005)) "is not relevant to the claims under consideration." While the claims on appeal may differ from the claims on appeal in *Capon v. Eshhar*, the Court took considerable effort to lay out the underlying framework for determining written description in other cases moving forward, and to clarify that written description, like enablement, must be determined on a case by case basis. Specifically, the standard for meeting the written description requirement and showing possession of the claimed invention, as articulated by *Capon v. Eshhar*, differs for every patent specification depending upon a number of factors, including the scientific knowledge in existence at the time of the invention, the skill in the art, the predictability of the claimed subject matter, and correlation of a described function to a known structure. Again, Appellants do not argue that the claims at issue in *Capon v. Eshhar* were the same as in the present case, rather that the written description standard articulated by the Court, when applied in the present case, is fully satisfied.

Specifically, as discussed further below, the maturity of the science and skill in the art at the filing date of the present invention were such that one of ordinary skill would have recognized that Appellants were in possession of the full-length human DEC-205 protein, based on the partial sequences described in the specification, as well as antibodies against the full-length protein (or any region or variants of the protein). As such, Appellants teachings in the specification, combined with the knowledge available in the art, demonstrate that Appellants were in full possession of the presently claimed invention at the time of filing.

5 . Isolation and Cloning of Proteins, and Generation of Antibodies Were Highly Mature Technologies at the Time of the Present Invention

Indeed, at the filing date of the present application (*i.e.*, in 1995), technologies for isolating, characterizing and cloning proteins were highly developed, as were technologies for generating antibodies against such proteins. For example, several well known techniques were available for cloning proteins, including human DEC-205, based on a given partial amino acid sequence of the protein (see, for example, page 20, line 30 through page 21, lines 1-19; as well as page 25, lines 25-31 through page 31, lines 1-16 of the parent application, USSN 09/586,704). Additionally, techniques for expressing cloned proteins (see, for example, page 31, lines 18-31 through page 35, lines 1-30 of the parent application, USSN 09/586,704) and for generating antibodies against the proteins were equally well known (see, for example, page 42, lines 23-31 through page 45, lines 1-19, and particularly page 42, lines 28-31 in the parent application, USSN 09/586,704). Once armed with a partial amino acid (*i.e.,* a peptide derived from a given protein), it was also well within the skill of the art to use these techniques to generate antibodies against such peptides and to isolate the full-length protein from its natural source.

Appellants specifically illustrated this in relation to mouse DEC-205. In particular, Appellants successfully isolated and characterize full-length mouse DEC-205 from whole murine thymus using mAb NLDC-145, an anti-mouse DEC-205 antibody (see page 63 of the parent application, USSN 09/586,704). Additionally, Appellants successfully raised antibodies against N-terminal peptides from mouse DEC-205 protein (see, for example, page 62, lines 26-32 and page 63, lines 1-15 of the parent application, USSN 09/586,704). This provides ***clear evidence*** that the partial human DEC-205 sequence described in the present disclosure put Appellants in possession of the complete DEC-205 protein and antibodies against the protein.

Additionally, in the present application, Appellants teach a partial (C-terminal) sequence (SEQ ID NO.:7) of human DEC-205 protein. Appellants further teach the highly homologous full-length sequence of mouse DEC-205 protein (SEQ ID NO.:10), along with an in-depth characterization of this protein (including its ability to deliver antigen to an active antigen processing compartment of dendritic cells). Appellants also describe well-known techniques for cloning proteins (including human DEC-205) based on a given partial amino acid sequence of the protein, expressing cloned proteins and generating antibodies against the proteins. Based on these teachings, it was well

within the skill of the art to have generated anti-DEC-205 antibodies. It was also well within the skill in the art to have generated full-length human DEC-205 protein, as well as variants of the human DEC-205 protein.

In fact, as evidenced by the Declaration by Dr. Michel Nussensweig (Exhibit A), the cloning techniques and techniques for generating antibodies described in the specification were ultimately successfully used to clone and isolate human DEC-205 and to produce antibodies against full-length human DEC-205. This provides clear evidence that Appellants were in fact indeed in possession of the claimed invention based on the descriptive text provided within the four corners of Appellants' originally filed disclosure.

C. Summary of Examiner's Rejection of Claims 6-9 Under 35 U.S.C. § 112, First Paragraph, as Failing to Comply with the Written Description Requirement

The Examiner has rejected claims 6-9 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that there is no support in the specification for a human DEC-205 protein comprising an amino acid sequence as set forth in SEQ ID NO.:7. The Examiner further asserts that, although the specification teaches that SEQ ID NO.:7 is a peptide derived from DEC-205, there is no support for a DEC-205 protein comprising the peptide wherein the molecule could have any amino acids in association with the aforementioned sequences recited in the claim.

D. Appellants' Response

For the many reasons discussed above in Section B, Appellants respectfully submit that the specification does indeed provide sufficient written description for human DEC 205 protein comprising SEQ ID NO:7, as recited in claims 6-9. Again, the mere fact that the disclosure teaches partial sequences for this protein does not alone mean that claims covering antibody conjugates, which bind to human DEC 205 comprising such sequences, lack written description. Whether claims 6-9 comply with § 112, first paragraph, depends on a variety of factors, as discussed above in relation to the previous rejection (Section B). The teachings in Appellants' specification, in combination with the skill and knowledge available in the art at the time the present application was filed, clearly demonstrate that Appellants possessed the invention recited in claims 6-9.

As previously discussed in detail, Appellants teach the partial C-terminal sequence of human DEC-205 (SEQ ID NO: 7). Based on this partial amino acid sequence, it was well within the skill of the art to have used known techniques to generate antibodies against this peptide, and to have predictably isolated the full-length protein or variants from its natural source. Accordingly, one of ordinary skill in the art could also have gained possession of a broad class of vaccine conjugates against any region of human DEC-205. In fact, the maturity of the science and skill in the art at the time of the present invention were such that those of ordinary skill in the art were routinely obtaining full-length proteins based on partial sequences, as well as predictably obtaining antibodies against such full-length proteins. This is specifically attested to in the Declaration submitted by Declaration by Dr. Michel Nussensweig (Exhibit A).

Further, as discussed above, the structure and function of human DEC-205 clearly correlates to that of mouse DEC-205, the characteristics of which (including full-length sequence) are described in detail in the present disclosure. Accordingly, the fact that Appellants provide an in-depth characterization of mouse DEC-205, including its full-length sequence, which clearly correlates to human DEC-205, provides further basis for fully meeting the Written Description requirement established by the Federal Circuit (*e.g.*, *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991), *The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997), *Carnegie Mellon University v. Hoffman-La Roche*, 541 F.3d 1115, and *Noelle v. Lederman*, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004)) and demonstrates possession of the claimed invention.

In sum, for at least the foregoing reasons, claims 6-9 fully comply with 35 U.S.C. § 112, first paragraph.

D. Summary of Examiner's Rejection of Claims 6-9 and 13-21 Under 35 U.S.C. § 112, First Paragraph, as Lacking Enablement

The Examiner has rejected claims 6-9 and 13-17 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner is of the opinion that the specification fails to disclose how to use the presently claimed methods for the *in vivo* treatment of disease in humans because it "provides no working

examples demonstrating that the instant invention can be used for the induction of tolerance/treatment of disease in vivo in humans or any animal model."

F. Appellants' Response

Appellants respectfully traverse this rejection for at least the following reasons. First and foremost, as discussed below, working examples are not required to enable a claimed method of treatment. Rather, the disclosure of working examples supporting a claimed invention is only one factor to be considered in determining whether the invention is enabled, and is not solely determinative of the issue.

1. The Existence of Working Examples

In response to the Examiner's suggestion that working examples are required to satisfy the enablement standard, Appellants respectfully note that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether *in vivo* data or working examples are disclosed (M.P.E.P. § 2164.02). In fact, the specification need not contain *in vivo* data or working examples if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)) and, importantly, ***if one of ordinary skill in the art would reasonably accept the supporting disclosure as being enabling based on the teachings and/or data that is provided*** (*In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)). In the present case, this standard is satisfied. Notwithstanding, contrary to the Examiner's assertion that the present specification ***fails to exemplify "that the instant invention can be used for the induction of tolerance/treatment of disease in vivo***," the specification ***does indeed provide multiple in vivo working examples*** (conducted in mouse models), to support the claimed invention. As provided in M.P.E.P. § 2164.02, "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention...***if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate***. As discussed below, mice were routinely used and accepted animal models at the time of filing. Accordingly, the Examiner must accept the present specification as enabling, unless there is evidence to the contrary.

Specifically, Appellants exemplify *in vivo* experiments in mice demonstrating that (1) antigen delivered to dendritic cells *in vivo* induces persistent T cell activation (see page 37, line 14 through page 38, line 7), (2) the absence of persistent T cell activation in mice injected with an anti-DEC-205 antibody fused to hen egg lysozyme (αDEC/HEL) is not due to a lack of antigen and, therefore, that targeting of antigen to DEC-205 causes persistent T cell activation (see page 38, lines 7-16), and (3) techniques for assessing dendritic cell function in mice receiving multiple doses of an anti-DEC-205 antibody fused to hen egg lysozyme (αDEC/HEL) (see page 38, line 18 through page 39, line 3). In view of these *in vivo* working examples and the fact that mice were (and still are) widely accepted animal models for assessing the clinical value of biological therapeutics, one of ordinary skill in the art would not reasonably doubt that the disclosed mouse data correlates with the claimed invention, nor that the presently claimed methods are fully enabled.

Indeed, as discussed below and evidenced by the references cited by the Examiner, mouse models have long been accepted in the field as being reasonably correlative of human treatment. While clinical studies in humans may ultimately be required to establish human treatments and therapeutic regimens, ***it is readily acknowledged in the art that the basic molecular principle behind a particular method of treatment is often first identified in a murine model***. In the present case, Appellants were the first to discover that tolerance can be initiated by targeting an antigen to dendritic cells using anti-DEC-205 antibodies, and to prove this in accepted animal models. The discovery of this molecular principle of tolerance was a typical and pivotal first step in establishing a pervasive concept for disease treatment.

2. Level of Predictability in the Art

The Examiner further asserts that *in vivo* treatment using the presently claimed methods is unpredictable in view of the teachings provided in the prior art. Specifically, the Examiner maintains that it is "unpredictable whether human disease can be treated via enhancing tolerance to a disease antigen" in view of Spack (*Expert Opin Investig Drugs.* 1997 Nov;6(11):1715-27), which teaches that attempts to treat Multiple Sclerosis by inducing tolerance to myelin have been unsuccessful and McKown *et al.* (*Arthritis Rheum.*1999 Jun;42(6):1204-8), which teach that attempts to treat Rheumatoid Arthritis by inducing tolerance to collagen have been unsuccessful.

Appellants respectfully disagree. Contrary to the Examiner's suggestion, these references cited by the Examiner do not support a lack of predictability for the presently claimed methods (*i.e.*, methods of enhancing the development of tolerance to a preselected antigen). In fact, quite the opposite. Specifically, McKown teach that daily oral treatment with bovine oral type II collagen (CII), when combined with existing therapy in patients with Rheumatoid Arthritis, did not result in a significant clinical improvement in the disease (see pages 1206-1207). However, McKown does not attribute this to a failure to induce tolerance to collagen, as suggested by the Examiner. Instead, the authors state that (1) "[t]he dosage of bovine CII that might induce bystander suppression in RA patients might be much lower than the" dosage used in the present study (see page 1207), (2) that the combination with other therapies, such as prednisone and nonsteroidal anti-inflammatory drugs, "may interfere with the induction of OT [oral tolerance]"(see pages 1207-1208) and (3) that "separate and apart from the drugs that RA patients take are possible agents in the foods of the diverse human diet that might interfere with GALT [gut-associated lymphoid tissue] processing of oral antigen" (see page 1208). Thus, while the combination therapies discussed in McKown were not successful in treating Rheumatoid Arthritis, the authors provide many rationales for this failure, **none of which implicate a failure to induce tolerance to collagen *per se***.

Moreover, importantly, the studies discussed by McKown did **not** involve targeting antigen (*e.g.*, collagen) to DEC-205 and dendritic cells and, as such, do not speak to the predictability of the **presently claimed invention**. Indeed, the presently claimed invention is based on the discovery that **targeting** of antigen to DEC-205 **enhances** and, therefore, **increases** the predictability of inducing an immune response. Spack teaches that there was not a statistical significance between Multiple Sclerosis ("MS") patients fed daily capsules of crude bovine myelin versus MS patients fed a placebo in treating their disease. However, the authors also note that those patients who received the myelin capsules "experienced fewer major exacerbations over the 1 year trial period than did patients fed placebo" (see page 1720). Therefore, Spack does, in fact, teach that vaccine treatment had a beneficial effect. Moreover, like McKown, the studies discussed by Spack did **not** involve targeting antigen (*e.g.*, collagen) to DEC-205 and dendritic cells. As such, the teachings of Spack do **not** speak to the predictability of the **presently claimed invention**. Indeed, it is demonstrated in the

present application that **targeting** of antigen to DEC-205 **enhances** and, therefore, **increases** the predictability of inducing an immune response.

Additionally, the Examiner asserts that the experimental data from mice provided in the specification is insufficient to enable human treatment *in vivo* in view of Tufveson *et al.* (Immunol Rev. 1993 Dec;136:99-109), and Mestas *et al.* (*J Immunol.* 2004 Mar 1;172(5):2731-8).

Appellants respectfully disagree that these references cast doubt on the predictability of *in vivo* treatment using the presently claimed methods. In fact, these references highlight the value of using animal models as a preliminary step in establishing a concept for disease treatment in humans.

Specifically, although Tufveson *et al.* (Immunol Rev. 1993 Dec;136:99-109) suggest that data from small animal models should not be the *sole basis* for "clinical decision making"... the authors also state that "it is evident that animal experiments to support modes of clinical action are warranted" (see page 101). Additionally, while Mestas *et al.* point out that mice and humans have obvious differences that "should be taken into account when using mice as preclinical models of human disease," the authors do not discount the value of mouse models and, in fact, state that their goal "is not to suggest that the mouse is an invalid model system for human biology" (see page 2731). Indeed, Mestas *et al.* teach that "[***m]ice are the experimental tool of choice for the majority of immunologists and the study of their immune responses has yielded tremendous insight into the workings of the human immune system***" and that "***mice are the mainstay of in vivo immunological experimentation and in many respects they mirror human biology remarkably well***" (see page 2731).

Moreover, contrary to the Examiner's suggestion that *in vivo* treatment using the presently claimed methods is unpredictable in view of teachings available in the art, Appellants respectfully note that there is ***substantial evidence*** in the art to demonstrate that a molecular principle ***can*** be predictably applied to the development of human therapeutics, once a principle has been identified and tested, for example, in an animal disease model (*e.g.*, an *in vivo* murine disease model). For example, Tysabri, an anti-VLA4 treatment for multiple sclerosis in humans, was presaged by Lawrence Steinman's anti-VLA studies of experimental allergic encephalomyelitis (EAE) in mice; see, for example, Yednock *et al.* (1992) *Nature* 356: 63-66, which concluded that "... therapies designed to interfere with alpha 4 beta 1 integrin may be useful in treating inflammatory diseases of the central nervous system, such as multiple sclerosis."

Similarly, Copaxone treatment for multiple sclerosis in humans, was presaged by Ruth Arnon's and Michael Sela's studies with copolymers in EAE in mice and the discovery of synthetic peptides as model antigens; see, for example, Teitelbaum D. *et al.* (1971) *Eur. J. Immunol.* 1: 242-248 which concluded that "[i]n its suppressive activity (the copolymer), it is as effective as the brain encephalitogen itself and thus may be of help both in studies of the mechanism of EASE and as a potential suppressive agent for EAE and other diseases of a similar nature." Additionally, FDA approved IL-2 treatment of cancer in humans was presaged by Steve Rosenberg's studies of mouse melanoma rejection in mice; see, for example, Rosenberg *et al.* (1985) *J. Exp. Med.* 161: 1169-1188, which concluded that "[t]he ready availability of high doses of recombinant human IL-2, and the demonstration of antitumor effects seen in animal models have led us to the initiation of the clinical trials of recombinant IL-2 in humans." Finally, CTLA-4 blockade, for which FDA approval is currently being sought as a new weapon in the treatment of cancer in humans, was presaged by Jim Allison's studies of anti-CTLA treatment of mouse tumors and the discovery of CTLA-4 as a counter-receptor for costimulatory B7 molecules in mice; see, for example, Leach *et al.* (1996) *Science* 271: 1734-1736, which concluded that "[t]hese results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effect immune responses against tumor cells."

These are but a few examples evidencing that a molecular principle ***can*** be predictably applied to the development of human therapeutics. Accordingly, it is clear that *in vivo* mouse models of experimentation are widely accepted as playing a key, initial role in the establishment of methods and therapeutics for treating human disease.

As such, it is clear that the working examples set forth in Appellants' specification provide more than sufficient evidence to enable the ordinarily skilled artisan to make and use the claimed invention using only routine experimentation. withdraw this rejection under 35 U.S.C. § 112, first paragraph. In sum, for at least the foregoing reasons, claims 6-9 and 13-21 fully comply with 35 U.S.C. § 112, first paragraph.

VIII. APPENDIX OF CLAIMS

A copy of the claims involved in the present appeal is set forth in Appendix A.

IX. CONCLUSION

In view of the above arguments, Appellant urges the Examiner and the Board to reconsider and withdraw the current rejections and to pass the claims to allowance.

Appellant believes that the pending application is in condition for allowance. If additional fees are due, please charge our Deposit Account No. 12-0080, under Order No. RUJ-001CNCPRCE2 from with the undersigned is authorized to draw.

Dated: November 22, 2010

Respectfully submitted,

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APPENDIX A: CLAIMS

6. **(Previously Presented)** A method for enhancing the development of tolerance to a preselected antigen for which tolerance is desired, in a mammal comprising exposing ex vivo or in vivo dendritic cells from said mammal to a conjugate comprising said preselected antigen covalently bound to an anti-human DEC-205 antibody or an anti-murine DEC-205 antibody that binds to human DEC-205 under conditions that promote dendritic cell quiescence, said human DEC-205 protein comprising an amino acid sequence as set forth in SEQ ID NO: 7, and wherein said preselected antigen is selected from the group consisting of allergens, autoantigens and antigens participating in allograft rejection.

7. **(Original)** The method of claim 6 wherein said preselected antigen is a peptide antigen or a protein antigen.

8. **(Original)** The method of claim 7 wherein said peptide or protein is conjugated to said antibody to DEC-205 by means of a cross-linking agent.

9. **(Original)** The method of claim 7 wherein a light chain or a heavy chain of said antibody to DEC-205, and said peptide antigen or protein antigen, are present on a single polypeptide chain.

13. **(Previously Presented)** A method for enhancing the development of tolerance to a preselected antigen for which tolerance is desired in a mammal, comprising exposing ex vivo or in vivo dendritic cells from said mammal to a conjugate comprising said preselected antigen covalently bound to an anti-human DEC-205 antibody, wherein the antibody is reactive with an amino acid sequence as set forth in SEQ ID NO: 7, under conditions that promote dendritic cell quiescence, wherein said preselected antigen is selected from the group consisting of allergens, autoantigens and antigens participating in allograft rejection.

14. **(Previously Presented)** A method for enhancing the development of tolerance to a preselected antigen for which tolerance is desired, in a mammal comprising exposing ex vivo or in vivo dendritic cells from said mammal to a conjugate

comprising said preselected antigen covalently bound to an anti-murine DEC-205 antibody, wherein the antibody is reactive with an amino acid sequence as set forth in SEQ ID NO: 7, under conditions that promote dendritic cell quiescence, and wherein said preselected antigen is selected from the group consisting of allergens, autoantigens and antigens participating in allograft rejection.

15. **(Previously Presented)** The method of either one of claims 13 or 14, wherein said preselected antigen is a peptide antigen or a protein antigen.

16. **(Previously Presented)** The method of either one of claims 13 or 14, wherein said peptide or protein antigen is conjugated to said antibody to DEC-205 by means of a cross-linking agent.

17. **(Previously Presented)** The method of either one of claims 13 or 14, wherein a light chain or a heavy chain of said antibody to DEC-205, and said peptide antigen or protein antigen, are present on a single polypeptide chain.

18. **(Previously Presented)** A method for enhancing the development of tolerance to a preselected antigen in a mammal, the method comprising exposing ex vivo or in vivo dendritic cells from the mammal to a conjugate comprising the preselected antigen bound to an anti-mouse DEC-205 antibody that cross reacts with human DEC-205 under conditions that promote dendritic cell quiescence, wherein the mouse DEC-205 protein comprises the amino acid sequence of SEQ ID NO: 10.

19. **(Previously Presented)** The method of claim 18, wherein the preselected antigen is selected from the group consisting of allergens, autoantigens and antigens participating in allograft rejection.

20. **(Previously Presented)** The method of claim 19, wherein the preselected antigen is bound to the antibody to DEC-205 by means of a cross-linking agent.

21. **(Previously Presented)** The method of claim 18, wherein a light chain or a heavy chain of the antibody to DEC-205, and the preselected antigen, are present on a single polypeptide chain.

APPENDIX B: EVIDENCE

Exhibit A is a copy of the Declaration by Dr. Michel Nussensweig, which was entered by the Examiner in conjunction with the Amendment and Response filed by Appellants on January 4, 2005.

Exhibit B is a copy of Guo *et al.* (Hum Immunol. 2000 Aug; 61(8):729-38), which was referenced in the Declaration by Dr. Michel Nussensweig and cited in an Information Disclosure statement (dated December 27, 2005) that was considered and initialed by the Examiner on March 19, 2006.

APPENDIX C: RELATED PROCEEDINGS

An Amendment and Response After Final was filed in the parent application, U.S.S.N.:09/586704, on October 25, 2010 and an Advisory Action issued on November 5, 2010.